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14. ABSTRACT

To test the idea that ovarian cancer arises from oviductal epithelium, spreads to the ovary, and presents as ovarian cancer, we generated a mouse model in which we can target genetic deletions to the oviductal epithelium. We are currently performing selective genetic deletion of ovarian cancer genes, such as TP53, Rb, and BRCA1 in oviductal epithelium in this mouse model. Interim analysis of the ongoing studies provided encouraging results. The mouse models we have generated using Ovgp1-CreERT2 are starting to generate ovarian and ductal tumors with a long latency of approximately 20 months. This long latency is similar to the natural history of human ovarian cancer as the majority of sporadic ovarian cancer is considered late onset. In addition, we also observed some tumor bearing mice have ascites and some don't reflecting the similar spectrum of disease presentation in human. Finally, we have provided these mouse models to three investigators so that they can use these models in their ongoing studies.

15. SUBJECT TERMS
Mouse models, fallopian epithelium, oviductal epithelium, BRCA1, Rb, TP53

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INTRODUCTION: In addition to previously accepted idea that epithelial ovarian cancer arises from surface epithelium of the ovary, recent evidence suggests that high-grade serous subtype of epithelial ovarian cancer may also arise from the fallopian epithelium [1, 2]. This shift in cell-of-origin for ovarian cancer has profound implication in the diagnosis, screen, and the pathobiology of ovarian cancer. Recent shift in the paradigm of the original sites of epithelial ovarian carcinogenesis suggest the fallopian epithelium as a potential site for high-grade serous subtype of ovarian cancer, endometriosis as putative precursors for clear cell and endometrioid subtypes of ovarian cancer, and transitional-type epithelium at the tubal-mesothelial junction as potential site of origin for mucinous ovarian cancer [3]. An essential component to advance our understanding of the pathobiology of high-grade serous ovarian cancer is to determine the exact site of origin where cancer arises because such tissue will serve as normal controls in any fundamental studies. However, appropriate mouse models to test a paradigm-shifting hypothesis that high-grade serous ovarian cancer may arise from fallopian tubal epithelium are lacking. Therefore, in this proposal we generated a mouse model to test the hypothesis that tubal epithelium could serve as an original site for ovarian cancer.

BODY: In last year report, we indicated progress in the following area:

Specific Aim 1

- Generated a mouse model targeting expression of Cre-ERT2 to the fallopian tube using Ovgp1 promoter.
- Generated floxed p53/Rb and floxed p53/BRCA1 mice
- Generating floxed p53/Rb; Ovgp1::Cre-ERT2 triple transgenic mice and floxed p53/BRCA1; Ovgp1::Cre-ERT2 triple transgenic mice
- Established immunohistochemical staining conditions for p53, Ki67, WT1, PAX2, PAX8, and cytokeratin

Specific Aim 2

- Concurrent with Specific Aim 1, we are generating triple transgenic mice to monitor tumor development at various time points. These experiments will continue with the approval by ACURO that is required as part of the institutional transfer.

In this year report, we continue to make progress in expanding the mice colonies needed for the study. We have completed the transfer of mice from previous institution (Mayo Clinic) to current institution (University of Kansas Medical Center). We obtained institutional approval to conduct animal research at the current institution (University of Kansas Medical Center). We also obtained approval from ACURO to continue the animal studies at the current location. Finally, we are beginning to observe tumor incidence in our mouse models. In particular, we are encouraged by the fact that p53/Rb floxed mice mediated by Ovgp1-CreERT2 mice are showing tumor incidence after 20 months. These mice bear ovarian and oviductal tumors and some have ascites, reflecting a wide spectrum of tumor development similar to human disease. In addition, this

long latency of tumor development (20 months) is also similar to human ovarian cancer as it mainly affects women in their late 50s and early 60s. These results suggest that our mouse models with a wide spectrum of disease presentation may closely model human disease and that these mouse models may prove useful in understanding the pathobiology of human ovarian cancer.

The best highlight of our ongoing studies is that we have provided these mouse models to three investigators (Dr. Virginia Shapiro at Mayo Clinic, Rochester, MN; Dr. Timothy Starr at University of Minnesota, MN; and Dr. Henning Walczak at Imperial College Landon, UK). In addition, we have completed Material Transfer Agreement and are in the processing of providing these models to Dr. Christoph Englert at Leibniz Institute for Age Research, Germany).

We would also like to point out that long latency of tumor development in our mouse models, although highly relevant to the natural history of human ovarian cancer, does impede the progress of research studies as there is a long delay between genetic deletions of target genes and tumor development. We are continuing to collect tumor specimens, and we will be performing immunohistochemical analysis of these tumor samples and additional studies involving transplantation of the ovaries.

During this reportable period, our progress was also impeded by the delay in transfer of grant from previous institution to current institution. In fact, the funding gap extended the entire reportable grant period (from August 2012 to August 2013). We completed the grant transfer on August 11, 2013.

KEY RESEARCH ACCOMPLISHMENTS:

- Provide the Ovgp1-CreERT2 mouse model to three investigators
- We are in the process of providing the mouse model to a fourth investigators
- We are beginning to observe tumor incidents (ovarian and ductal tumors) in these mice after 20 months of latency
- Slow latency and spectrum of tumors (some with or without ascites) indicate the mouse model may faithfully reproduce human disease

REPORTABLE OUTCOME: Studies are ongoing, and interim analysis of data indicates that a promising mouse model that may faithfully reproduce human disease. In addition, we are continuing to accrue tumor tissues from these mice. In addition, we have generated two primary cultures from these tumors so that we can perform essential in vitro studies to understand the nature of these tumor cells. We plan to report these findings in upcoming AACR Annual meeting in 2014. We do not have any paper or poster presentation during the reportable grant period.

CONCLUSION: The study period starts from the August 2012 to August 2013. During that period, we continued to maintain and expand the mouse colonies to initiate studies as outlined in the SOW. We completed the transfer of grant on August 11, 2013 at the tail end of this reporting period. Although this funding gap has affected the progress of research studies, it did not severely impede the progress because the mouse model shows delayed tumor development similar to human disease. We provided the mouse models to three investigators and in the process of providing the model to the fourth investigator. We did not delay the distribution of this mouse model to others until we have our first publication in this mouse model because we do not want their research progress delayed by our insignificant desire to have the first publication. We hope that our encouraging results showing that delayed tumor development in these mice may model natural history of human ovarian cancer may encourage more investigators to start working with our mouse model to advance our understanding of this deadly malignancy.

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